What is the current state of play of CAR T-cell therapy for B-cell malignancies? Focus on patient selection, safety and new indications

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Agenda

- Selecting patients for CAR T-cell therapy – Where are we now?
- Managing CAR T-cell therapy-related adverse events – What is the current standard?
- Future indications for CAR T-cell therapy – How will they change the treatment paradigm?

CAR, chimeric antigen receptor.

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Patient eligibility considerations for CAR T-cell therapy in DLBCL

Key eligibility criteria in JULIET and ZUMA-1[1–5]

Patient factors

- Age ≥18 years
- ≥2 prior therapy lines
- ECOG PS: 0 or 1
- No existing or suspected infection

Medical history

- No prior CAR-T/anti-CD19 therapy
- No prior allo-HSCT
- No prior or concurrent malignancy (some exceptions)
- No active CNS involvement of DLBCL (JULIET)
- No prior/active CNS disease (ZUMA-1)

Disease status

- R/R disease
- Histologically confirmed diagnosis

Other

- Immunosuppressants stopped >4 weeks prior to enrolment

Beyond the trial setting?[5–8]

Patient factors

- Physical condition
- Performance status
- Prior lines of therapy
- Active infection

Medical history

- History of CNS disease
- History of cancer
- Co-morbidities

Disease status

- NHL histology
- Tumour volume
- CNS involvement

Other

- CAR T-cell product attributes
- Treatment logistics
- Need for urgent therapy

allo-HSCT, allogeneic haematopoietic stem cell transplant; CAR, chimeric antigen receptor; CD, cluster of differentiation; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group; NHL, non-Hodgkin lymphoma; PS, performance status; R/R, relapsed/refractory.

1. ClinicalTrials.gov. NCT02445248. Available at: clinicaltrials.gov/ct2/show/NCT02445248 (accessed 17 February 2021); 2. ClinicalTrials.gov. NCT02348216. Available at: clinicaltrials.gov/ct2/show/NCT02348216 (accessed 17 February 2021); 3. Schuster SJ, et al. *N Engl J Med.* 2019;380:45–56; 4. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531–44; 5. Yakoub-Agha I, et al. *Haematologica.* 2018;105:297–316; 6. Smith S, et al. *Am J Hematol.* 2019;94:E117–20; 7. Locke FL, et al. *Blood Adv.* 2020;4:4898–911; 8. Kansagara A, et al. *Am Soc Clin Oncol Educ Book.* 2020;40:e27–34.

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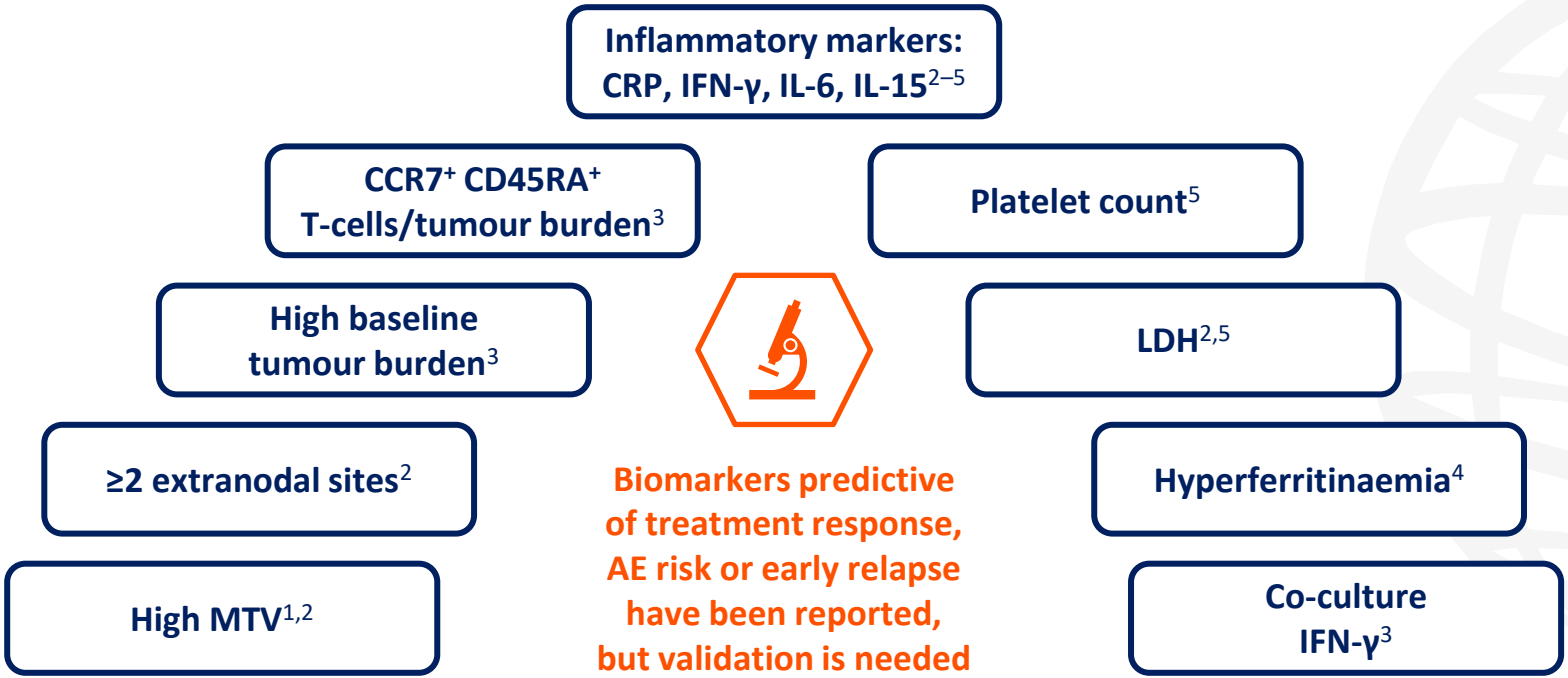
Potential biomarkers to guide patient selection



AE, adverse event; CCR, chemokine receptor; CD, cluster of differentiation; CRP, C-reactive protein; IFN, interferon; IL-interleukin; LDH, lactate dehydrogenase; MTV, metabolic tumour volume.

1. Dean EA, et al. *Blood Adv*. 2020;4:3268–76; 2. Vercellino L, et al. *Blood Adv*. 2020;4:5607–15; 3. Locke FL, et al. *Blood Adv*. 2020;4:4898–911; 4. Turtle CJ, et al. *Sci Transl Med*. 2016;8:355ra116; 5. Du M, et al. *Biomark Res*. 2020;8:13.

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Recognizing AEs related to CAR T-cell therapy

The severity and tempo of AEs associated with CAR T-cell therapies are beginning to be better understood, and this may guide vigilance and optimize clinical management[1–6]

Short term (infusion to day +28)

Rapid *in vivo* CAR T-cell proliferation is associated with potentially life-threatening toxicities

CRS

- Most frequent complication (58–93%)*
- Typical onset: 1–14 days post-infusion

ICANS

- Second most frequent complication (21–67%)*
- Typical onset: 1–34 days post-infusion
- May progress over hours or days

Infection

- Bacterial infections most common
- Typically present within 30 days

Medium term (day +28 – day +100)

Neutropenia, thrombocytopenia and anaemia are common, showing slow resolution over months

Delayed CRS

- Delayed macrophage activation syndrome and CRS may occur

B-cell aplasia

- Frequent on-target, off-tumour toxicity in responding patients
- Results in hypogammaglobulinemia and may persist for years

Infection

- ≥Day 30, viral infections predominate
- Later infections may reflect immunoglobulin deficiency and/or lymphopenia

*Ranges based on all-grade CRS or ICANS data reported from clinical trials of EMA-approved indications of axicabtagene ciloleucel (DLBCL and PMBCL) and tisagenlecleucel (DLBCL and B-cell ALL), and the conditionally approved EMA indication of brexucabtagene autoleucel (MCL).

AE, adverse event; ALL, acute lymphoblastic leukaemia; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; ICANS, immune-effector cell-associated neurotoxicity syndrome; MCL, mantle cell lymphoma; PMBCL, primary mediastinal large B-cell lymphoma.

1. Yakoub-Agha I, et al. *Haematologica.* 2018;105:297–316; 2. Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625–38; 3. Riedell PA, Bishop MR. *Ther Adv Hematol.* 2020;11: 2040620720902899; 4. Schuster SJ, et al. *N Engl J Med.* 2019;380:45–56; 5. Maude SL, et al. *N Engl J Med*. 2018;378:439–48; 6. Wang M, et al. *N Engl J Med*. 2020;382:1331–42.

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Long term: 'Late-effects'
(>day +100)

Given only a small cohort of patients have had ≥2 years' follow-up, little is currently known, but main complications include:[1–3]

- **Prolonged cytopenias**
- **Hypogammaglobulinemia**
- **Theoretical concerns:**
  - Risk of secondary malignancy
  - Autoimmune disease
  - Neurological disease
  - Transmission to the germline

CAR T-cell treatment centre has a duty of care to coordinate appropriate local follow-up for late-effects monitoring over the long term

AE, adverse event; CAR, chimeric antigen receptor.

1. Yakoub-Agha I, et al. *Haematologica.* 2018;105:297–316; 2. Jin C, et al. *EMBO Mol Med.* 2016;8:702–11;
3. European Medicines Agency. 2006. Available at: www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-7.pdf (accessed 17 February 2021).

Harmonizing grading and safety management protocols

ASTCT consensus grading systems[1]

CRS

Grade 1	Grade 2	Grade 3	Grade 4
Temperature ≥38°C *with:*			
No hypotension	**Hypotension** Not requiring vasopressors	**Hypotension** Vasopressor ± vasopressin	**Hypotension** Multiple vasopressors (excluding vasopressin)
	and/or	*and/or*	*and/or*
No hypoxia	**Hypoxia** Low-flow nasal cannula/blow-by	**Hypoxia** High-flow nasal cannula, face mask, non-rebreather mask or Venturi mask	**Hypoxia** Requiring positive pressure

Grade 2 CRS: Alert ICU if no response to tocilizumab

In addition to symptomatic measures, tocilizumab or corticosteroids may be administered[2]

ICANS

Grade 1 ICE 7–9	Grade 2 ICE 3–6	Grade 3 ICE 0–2	Grade 4 ICE 0
• Drowsiness but patient awakens spontaneously	• Drowsiness but awakens to voice	• Awakens only to tactile stimulus • Clinical or electrographic seizure • Focal or local oedema on neuroimaging	• Unable to rouse patient • Unable to ICE-assess • Prolonged or repetitive electrographic seizures • Deep focal motor weakness • Diffuse cerebral oedema on neuroimaging

Alert ICU with rapid access to neurological expertise (grades 2–4, transfer to ICU)[1,2]

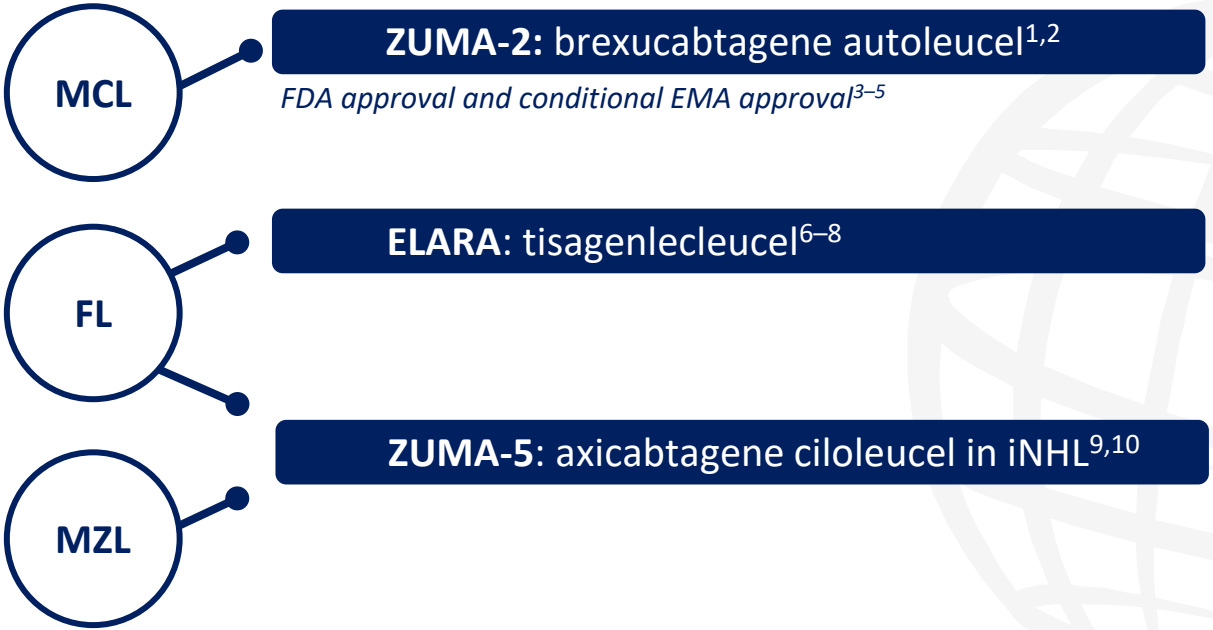
Management may require cross-sectional imaging, electroencephalograph, and CSF examination[2]

ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; CSF, cerebrospinal fluid; ICANS, immune-effector cell-associated neurotoxicity syndrome; ICE, immune-effector cell-associated encephalopathy; ICU, intensive care unit.

1. Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625–38; 2. Yakoub-Agha I, et al. *Haematologica.* 2018;105:297–316.

Exploring clinical potential in emerging indications

Ongoing trials are investigating the safety and efficacy of CAR T-cell therapies in indications with high unmet treatment needs



CAR, chimeric antigen receptor; EMA, European Medicines Agency; FDA, US Food and Drug Administration; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.

1. Wang M, et al. *N Engl J Med*. 2020;382:1331–42; 2. ClinicalTrials.gov. NCT02601313. Available at: clinicaltrials.gov/ct2/show/NCT02601313 (accessed 17 February 2021); 3. EMA. 2021. Available at: www.ema.europa.eu/en/medicines/human/EPAR/tecartus#product-information-section (accessed 17 February 2021); 4. EMA. 2020. Available at: www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-12-15-october-2020 (accessed 17 February 2021); 5. FDA. 2020. Available at: www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/tecartus-brexucabtagene-autoleucel (accessed 17 February 2021); 6. Dickinson M, et al. *J Clin Oncol*. 2019;37:TPS7573; 7. Fowler NH, et al. *Blood*. 2020;136:1–3; 8. ClinicalTrials.gov. NCT03568461. Available at: clinicaltrials.gov/ct2/show/NCT03568461 (accessed 17 February 2021); 9. Jacobson C, et al. Presented at: 2020 ASCO Virtual Scientific Program, location, 29-31 May 2020. Abstr 8008; 10. ClinicalTrials.gov. NCT03105336. Available at: clinicaltrials.gov/ct2/show/NCT03105336 (accessed 17 February 2021).

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Key efficacy outcomes for emerging indications

MCL

ZUMA-2:* brexucabtagene autoleucel[1,2]

Primary efficacy analysis (N=60)	Estimated 12 months' median follow-up for efficacy	**ORR 93%** (95% CI 84–98) **CR 67%** (95% CI 53–78)	**Estimated 12-month PFS 61%** (95% CI NS)

FL

ELARA:* tisagenlecleucel[3–6]

ITT efficacy analysis (N=52)	9.9 months' median follow-up for efficacy	**ORR 82.7%** (95% CI 69.7–91.8) **CR 65.4%** (95% CI 45.1–82.4)	**6-month PFS 73.2%** (95% CI 58.2–83.5)

MZL

ZUMA-5:* axicabtagene ciloleucel in iNHL[7,8]

Primary efficacy analysis iNHL (N=146) (FL n=124; MZL n=22)	17.5 months' median efficacy follow-up (iNHL=104)	**ORR 92%** (95% CI NS) **CR 76%** (95% CI NS)	**Estimated 12-month PFS 74%** (95% CI 63–82)

*Timing of first PET scan post-infusion varies between trial protocols.

CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; ITT, intent to treat; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NS, not specified; ORR, objective response rate; PET, positron emission tomography; PFS, progression-free survival.

1. Wang M, et al. *N Engl J Med.* 2020;382:1331–42; 2. ClinicalTrials.gov. NCT02601313. Available at: clinicaltrials.gov/ct2/show/NCT02601313 (accessed 17 February 2021); 3. Dickinson M, et al. *J Clin Oncol.* 2019;37:TPS7573; 4. Fowler NH, et al. *Blood.* 2020;136:1–3; 5. Salles G. *Clin Adv Haematol Oncol.* 2021;19:1-20; 6. ClinicalTrials.gov. NCT03568461. Available at: clinicaltrials.gov/ct2/show/NCT03568461 (accessed 17 February 2021); 7. Jacobson C, et al. *Blood.* 2020;136:40–1; 8. ClinicalTrials.gov. NCT03105336. Available at: clinicaltrials.gov/ct2/show/NCT03105336 (accessed 17 February 2021).

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